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Evidence for Independent Feedback Control of Horizontal and Vertical Saccades from Niemann-Pick Type C Disease

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We measured the eye movements of three sisters with Niemann-Pick type C disease who had a selective defect of vertical saccades, which were slow and hypometric. Horizontal saccades, and horizontal and vertical pursuit and vestibular eye movements were similar to control subjects. The initial movement of oblique saccades was mainly horizontal and most of the vertical component occurred after the horizontal component ended; this resulted in strongly curved trajectories. After completion of the horizontal component of an oblique saccade, the eyes oscillated horizontally at 10–20 Hz until the vertical component ended. These findings are best explained by models that incorporate separate feedback loops for horizontal and vertical burst neurons, and in which the disease selectively affects vertical burst neurons. Published by Elsevier Science Ltd

Niemann-Pick Eye movements Saccades Brainstem

INTRODUCTION

A variety of genetic diseases cause characteristic disorders of eye movements (Leigh & Zee, 1991). One such condition is Niemann-Pick type C disease (NPC), a cholesterol lipidosis (Pentchev *et al.*, 1985; Vanier *et al.*, 1991), with an identified genomic marker on chromosome 18 (Carstea *et al.*, 1993). Clinically, NPC may have its onset in childhood or adolescence (Higgins *et al.*, 1992) and is characterized by intellectual impairment (often presenting as poor school performance), ataxia, dysarthria, and impaired vertical gaze. The clinical features and manner of progression of the gaze disorder have been previously described (Neville *et al.*, 1973; Breen *et al.*, 1981; Cogan *et al.*, 1981a,b; Fink *et al.*, 1989; Shawkat *et al.*, 1994). NPC starts with loss of voluntary vertical saccades (down more than up) and fast phases of vertical optokinetic nystagmus; it later involves horizontal saccadic movements and convergence. This picture contrasts with certain other lipid storage disorders, such as forms of Gaucher's disease, in which horizontal saccades are selectively impaired early in the course (Cogan *et al.*, 1981b).

Despite the numerous clinical reports of NPC, and substantial progress in understanding the underlying biochemical disorder, there have been few attempts to quantify the gaze disorder using reliable methodology. We set out to systematically characterize the eye movements in NPC, with the goal of obtaining data that could be used to test current models for the coordination of horizontal and vertical gaze. To this end, we used a strategy of comparing horizontal and vertical components of oblique eye movements. Preliminary results have been published as an abstract (Rottach *et al.*, 1995).

PATIENTS AND METHODS

Patient 1

Like her three sisters, this 29-yr-old woman was born after an uncomplicated, full-term gestation and delivery to nonconsanguineous parents of Italian ancestry. She was healthy as an infant and attained developmental milestones normally. She was active in sports at high school, but her academic function was below average. At age 20, she first noticed dysarthria and hand incoordination. Over the following years, she gradually developed increasing body sway, poor balance with frequent falls, and dysphagia. The family history of illness was remarkable for vascular disease, and for a maternal aunt with an abnormal gait and unspecified mental disease. By

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age 26, her examination was notable for mild, generalized cognitive impairment, vertical gaze palsy affecting predominantly downward saccades, bradykinesia and mild dystonic posturing of the extremities. Electrocardiogram, electromyography, magnetic resonance imaging of the head, lumbar myelogram, and routine cerebrospinal fluid examination were all normal. Brainstem auditory evoked responses were abnormal on the right side, lacking an identifiable I and III wave, and audiogram revealed mild to moderate bilateral high frequency hearing loss. By age 28, her vertical saccades were restricted to only a few degrees below the horizontal meridian, and slightly limited above it. During attempted oblique saccades, curved trajectories were evident, due to slower vertical components. Downward smooth pursuit was slow and incomplete, but the vestibulo-ocular reflex was normal in both planes. Stimulation with a hand-held optokinetic tape induced nystagmus in the horizontal plane, but in the vertical plane her eyes followed the stimulus without quick phases. Convergence was intact. Finger tapping was slowed and during heel–knee–shin testing, there was leg clumsiness with dystonic toe movements. The diagnosis of NPC was confirmed by marked deficiency of cultured skin fibroblasts to intracellularly esterify exogenously supplied cholesterol [144 $\pm$ 24 pmol cholesterol ester formed per mg protein (cef/mgp), normal: 3432 $\pm$ 1729] and accumulation of unesterified cholesterol in the perinuclear region of fibroblasts, as demonstrated by the presence of filipin-stained cells.

Patient 2

This 25-yr-old woman was first evaluated because of coughing and choking. She had been working as a secretary. As a child, she was healthy but less intelligent than her sisters. In retrospect, her speech had become progressively slowed over the recent years. On examination, she had limitation of upgaze and vertical saccades appeared slow, both up and down. Oblique saccades had a curved trajectory. Her speech was slurred with poor articulation. There was slight ataxia on finger-to-nose testing with a dystonic component to the initial movements. She could not sustain steady balance with her eyes closed, or on tandem testing. A decreased ability to esterify exogenously supplied cholesterol (366 $\pm$ 29 pmol cef/mgp), positive filipin staining and elevated liver enzymes confirmed the diagnosis of NPC. Cranial computed tomography showed some cortical and cerebellar atrophy.

Patient 3

This 22-yr-old woman had noticed progressive dysphagia, slowing of her speech, poor hand coordination and emotional lability since the age of 18. She also had participated in sports. At age 15, she developed a peculiar swinging of the hips when walking. At age 17, her handwriting had begun to deteriorate. On examination at age 19, she showed inattention and impaired verbal fluency. She had diffuse bradykinesia with some superimposed dystonic movements, mild ataxia, and some dysmetria. Deep tendon reflexes were brisk. She was unable to generate downward saccades without blinking. Vertical saccades were both small and slow, but horizontal saccades were judged to be of normal velocity with mild hypometria. Diagonal saccades had a curved trajectory. Horizontal and vertical smooth pursuit and vestibular eye movements were preserved. Deep tendon reflexes were 1 – 2 + in the upper and 3 + in the lower extremities. Finger-to-nose testing was slow, there was mild rebound phenomenon in the upper extremities, and heel–knee–shin testing suggested clumsiness. Her gait was notable for peculiar elevation and rolling forward at the hips. Fibroblast cholesterol esterification level was abnormal (187 $\pm$ 30 pmol cef/mgp) and filipin staining positive. All three affected sisters had been taking cholesterol-lowering agents (lovastatin 120 mg/day, niacin 3 g/day, cholestyramine 18 g/day) and a low-cholesterol diet (Patterson *et al.*, 1993a), with variable compliance, for 1 yr.

The unaffected sister

The unaffected sister of patients 1–3 was 30 yr old, and worked as a police officer. Her ability to esterify exogenously supplied cholesterol was normal (2693 $\pm$ 275 pmol cef/mgp), although her filipin staining showed some positive cells, a pattern seen with some heterozygotes (Kruth *et al.*, 1986). As *normal controls* three age-matched healthy subjects (male aged 24, and females aged 26 and 29 yr) were tested with the same paradigms. All patients and subjects gave informed consent in accordance with the Declaration of Helsinki.

Eye movement measurements

Eye and head movements were recorded using the magnetic search coil technique (Grant *et al.*, 1992). Blinks were monitored by DC electro-oculography. Search coils were calibrated prior to each experimental session using a protractor device. Coil signals were filtered (bandwidth 0–90 Hz) prior to digitization at 333 Hz (for saccades), 300 Hz (for step-ramps) or 200 Hz (for smooth pursuit of sinusoidal stimuli, and vestibular testing).

Experimental stimuli. The visual stimulus was either an Amsler grid subtending 20 $\times$ 20 deg, or a red laser spot; they were rear-projected onto a semitranslucent tangent screen 1.2 m in front of the patients. The position of the laser spot was determined by an X–Y mirror galvanometer (General Scanning DX2003) under the control of a 80486 computer. *Saccades* were made in response to laser-spot jumps to positions on concentric circles corresponding either to a 10 deg or to a 20 deg gaze amplitude. The target jumped randomly from the midposition to eight different locations on this circle (e.g. 0 deg, 45 deg, 90 deg, etc.). The timing of target jumps was predictable, but its direction of movement was not. Each centrifugal step was followed by a centripetal step back to the midposition. *Smooth pursuit* was tested using step-ramp or sinusoidal motion of the laser spot. Step-

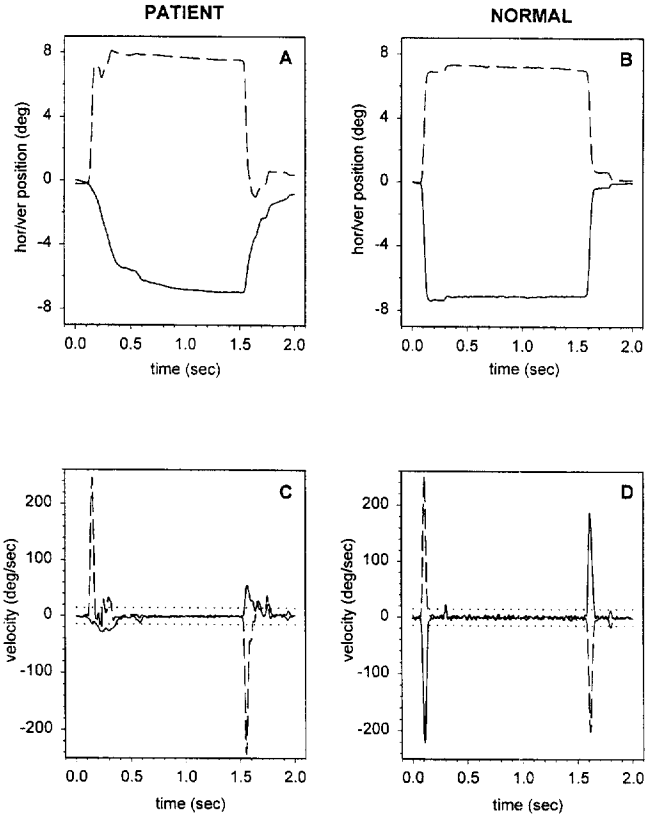

FIGURE 1. Representative plots of the horizontal (– – –) and vertical (——) components of oblique saccades from Patient 2 and Subject 2. (A) and (B) position data; (C) and (D) corresponding velocity traces. The dotted line indicates ±15 deg/sec, which was the threshold generally used for identifying saccade onset and offset. Positive deflections indicate rightward and upward eye rotations in this and subsequent figures. The patient showed marked slowing of vertical components of the saccades, more so downward.

ramp stimuli (Rashbass, 1961; Tychsen & Lisberger, 1986) tested smooth pursuit initiation and consisted of a 2 deg step in one direction from midposition, followed by a 10 deg/sec ramp in the opposite direction. The duration of the ramp was randomized between two and three seconds; in addition, the direction of the ramp was varied among the same eight directions used to test saccades. Sustained smooth pursuit was tested using sinusoidal target motion at 0.3 Hz, ±20 deg, directed horizontally, vertically, or obliquely (up left to down right, and vice versa). *Gaze stability during active head rotations* in the horizontal and vertical planes was determined by measuring the gain of compensatory eye movements in complete darkness while imagining the target at the midposition of the screen, and as subjects fixated the stationary laser target (Grant *et al.*, 1992).

Data analysis. Analysis was performed using interactive programs. *Saccades*: the horizontal and vertical components of each movement were analyzed separately. Since many saccades were slow, and performed in multiple steps, the determination of onset and end was sometimes difficult. In order to establish criteria for identifying these temporal characteristics, we reviewed the experience of other investigators. Most had used a velocity criterion only (Baloh *et al.*, 1975; Bahill *et al.*, 1981; Abel *et al.*, 1983; Collewijn *et al.*, 1988a; Van Opstal & Van Gisbergen, 1987; Johnston *et al.*, 1993; Boetzel *et al.*, 1993); some used the position signal (Sharpe & Zackon, 1987), and others a combination of position and velocity signal (Becker & Jürgens, 1990). Newsome *et al.* (1985) used a combination of velocity and acceleration criteria to identify saccades during responses to step-ramp stimuli by monkeys. Because our patients had very slow vertical saccades (Fig. 1), we chose a velocity threshold of 15 deg/sec for saccade onset and offset. These data points were found automatically by the program but each was also confirmed interactively. In < 5% of cases, small vertical movements did not exceed this velocity threshold, and these cases were determined to be saccades from the eye acceleration record. To be called a saccade, the movement needed to show the typical acceleration–deceleration double-peak, with both peaks exceeding 250 deg/sec^2. Saccade onset was set when the acceleration exceeded 250 deg/sec^2 and saccade end was set when the deceleration exceeded 250 deg/sec^2. The latency of a saccade was determined as the time between the target jump and the onset of the saccade (gaze velocity exceeding 15 deg/sec). We measured the amplitude and peak velocity of each saccade, and the time taken to reach peak velocity. The saccadic gain was calculated as the ratio of the amplitude of the first saccade to the amplitude required to foveate the target. In the case of multistep saccades, we measured the first movement since it represents the so-called open loop condition during which no visual feedback is available. For oblique saccades, the initial and final angle of the trajectory was calculated. For the 'initial angle', we used the horizontal and vertical positions at the saccade onset and at the time of peak velocity. For the 'final angle', we took the horizontal and vertical positions at onset and at the end of the saccade [see Becker & Jürgens (1990)]. In addition, we wanted to know which position the eye finally reached before the target jumped again. Therefore, we measured the eye position after completion of the whole refixation movement (both horizontal and vertical) including all corrective saccades and glissades (the 'reached' angle).

Responses to step-ramp stimuli. In order to determine the onset of the smooth pursuit movement we employed a regression technique (Carl & Gellman, 1987; Morrow & Sharpe, 1993). First the digitized gaze position signals were low-pass filtered with a Blackman window (bandwidth 0–20 Hz) and then differentiated to obtain the eye velocity signal. A first regression line, based on 220 msec of data was fit along the baseline (zero velocity). A second regression line was fit along the velocity signal of the smooth pursuit movement. The calculation was based on at least 60 msec of recording time, beginning where gaze velocity exceeded 3 SDs above the baseline and ending where gaze velocity exceeded the limit for saccades (15 deg/sec). Onset of the presaccadic smooth pursuit was determined at the point

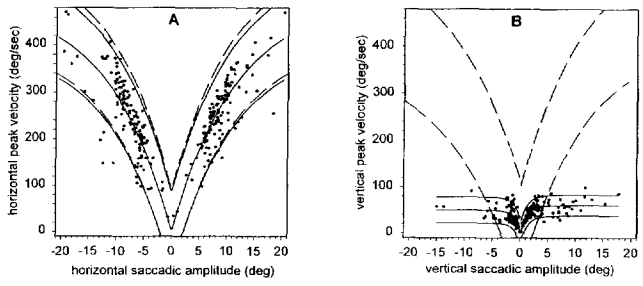

FIGURE 2. Comparison of relationship between saccadic amplitude and peak velocity for (A) horizontal and (B) vertical saccades. Individual horizontal and vertical components of saccades from the three patients are shown as data points. The 95% confidence levels for the population of saccades from the normal subjects are shown as dashed lines. The regression line and 95% confidence limits for saccades from patients are shown as solid lines. Note that the patients' horizontal saccades are similar to the normal subjects, but vertical saccades are smaller and slower in the patients.

where these two regression lines intersected. Responses with < 60 msec of smooth pursuit before the first catch-up saccade occurred were not used to calculate presaccadic smooth pursuit. If the presaccadic smooth pursuit lasted longer than 100 msec, we used only the first 100 msec for the analysis in order to stay within the open-loop response. Average eye acceleration was determined within this segment (Tychsen & Lisberger, 1986). Furthermore, we analyzed the first catch-up saccade, determining its beginning and end by the same criteria as described above for the saccade paradigm. The angle of the initial smooth pursuit movement and the first corrective saccade were calculated as described above. The position error (difference between eye and target position) at the end of the saccade was also calculated. For step-ramp responses without presaccadic smooth pursuit, we determined the postsaccadic smooth pursuit velocity (mean velocity during the 60 msec immediately after the first catch-up saccade) as a criterion of assessment of the initial smooth pursuit response. For all trials we measured maximum smooth eye velocity.

Sinusoidal smooth pursuit responses and gaze stability during head rotations. Saccades and quick phases of nystagmus were removed from the recording by windowing eye velocity signals (Barnes, 1982). The gain of the smooth pursuit response, and the gain of compensatory eye movements during head rotations were determined, for each test condition, as previously described (Grant *et al.*, 1992). For all statistical comparisons, the Mann–Whitney rank sum test was used.

RESULTS

Fixation

With the eyes near primary position or at eccentric positions in the orbit, fixation was normal with no nystagmus or saccadic intrusions. Horizontal gaze range was unrestricted. The vertical gaze range was restricted to about ±20 deg for all three patients.

TABLE 1. Summary of dynamic properties of saccades

	Patients	Normals
Asymptotic peak velocity[*]		
All horizontal saccades	496 (30)	505 (22)
Upward saccades	61 (2)	527 (44)
Downward saccades	50 (3)	515 (55)
Saccadic gain[†]		
All horizontal saccades	0.93[‡] (0.23/2.27)	0.92 (0.45/1.38)
Upward saccades	0.41[**¶] (0.05/1.19)	0.91[§] (0.50/1.15)
Downward saccades	0.15[**¶] (0.02/0.90)	1.00[§] (0.67/1.32)
All vertical saccades	0.24[**‡] (0.02/1.19)	0.95 (0.50/1.32)
Latencies[†]		
Horizontal	120[**††] (86/109)	148 (84/286)
Vertical	150[††] (85/220)	160 (80/245)
Oblique[‡‡]	142 (82/285)	153 (80/278)

[*]Coefficients for asymptotic peak velocity of the experimental curve fit in deg/sec; values in parenthesis show standard error.
[†]Median with range shown in parentheses; latencies are in msec.
[‡]Difference between gain of horizontal and vertical saccades in patients was significant, $P < 0.0001$, Mann–Whitney rank sum test.
[§]Difference between gain of upward and downward saccades in normals was significant, $P < 0.0001$, Mann–Whitney rank sum test.
[¶]Difference between gain of upward and downward saccades in patients was significant, $P < 0.0001$, Mann–Whitney rank sum test.
[**]Difference between normals and patients was significant, $P < 0.0001$, Mann–Whitney rank sum test.
[††]Difference between horizontal and vertical latencies for patients was significant, $P < 0.0001$, Mann–Whitney rank sum test.
[‡‡]Values are mean of horizontal and vertical components.

Saccades

All three patients showed similar abnormalities. Analysis of the *peak velocity/amplitude* ('main sequence') relationships showed that vertical saccades were slow as were vertical components of oblique saccades. In contrast, horizontal saccades and horizontal components of oblique saccades were of normal velocity. Figure 1 compares an oblique saccade from Patient 2 and from Subject 2. We found no significant difference between the peak velocity of purely horizontal or vertical saccades and corresponding components of oblique saccades. Therefore, we pooled horizontal and vertical components of oblique saccades with purely horizontal and vertical saccades, respectively. The relationship between peak velocity and amplitude for horizontal and vertical saccades from the three patients is summarized in Fig. 2 and compared with the 95% confidence limits for the normal subjects. The nonlinear regression line in that figure was fitted to the data using the equation

$$\text{peak velocity} = V_{max} \times (1 - e^{-\text{Amplitude}/C})$$

where V_{max} is the asymptotic peak velocity and C is a constant (Abel *et al.*, 1983). Figure 2 shows that the asymptotic peak velocity for horizontal saccades was similar for the patients and normal subjects. For vertical saccades, however, the asymptotic peak velocity was

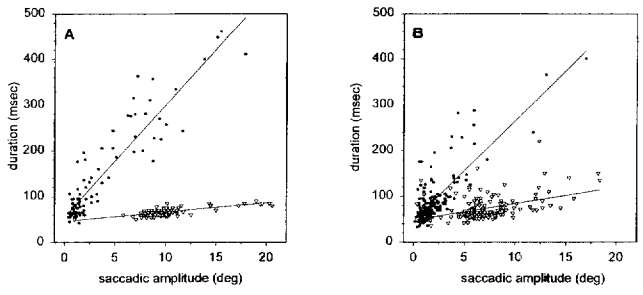

FIGURE 3. Comparison of relationship between duration and amplitude of saccades from the three patients. Saccades and components are represented by △ (horizontal) and ● (vertical). In (A), purely horizontal or vertical saccades are plotted; note the different regression lines. In (B) horizontal and vertical components of oblique saccades are shown. Note how some horizontal components of oblique saccades are prolonged ('stretched') during oblique movements, but the large difference between the durations of horizontal and vertical components is still apparent.

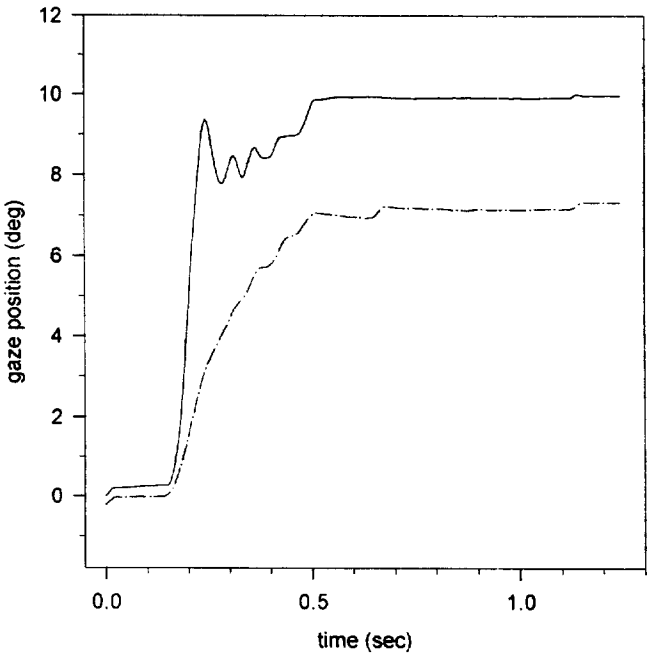

FIGURE 4. An example of horizontal oscillations occurring after the horizontal component (——) of an oblique saccade had ended, but while the vertical component (– · –) was still going on.

about one tenth of that for normal subjects, and downwards saccades had lower peak velocities than upwards saccades. The values for V_{max} from normal subjects and patients are summarized in Table 1.

The *saccadic duration* for purely vertical saccades was greater than that for purely horizontal saccades of similar size [Fig. 3(A)]. However, when oblique saccades were considered [Fig. 3(B)], it became evident that horizontal components of oblique saccades were occasionally prolonged ('stretched'). In many saccades the horizontal component was completed before the vertical. In these cases the eye did not remain motionless horizontally, but oscillated with a frequency of 10–20 Hz and an amplitude of 0.2–1.5 deg until the vertical component ended (Fig. 4).

The data on *saccadic gain* are summarized in Table 1. For patients and normals, there was no significant difference between the gains of purely horizontal saccades and horizontal components of oblique saccades. Furthermore, there was no significant difference between the gains of vertical components (either up or down) of oblique saccades and purely vertical saccades. Thus, for example, the presence of a small, slow vertical component did not significantly affect the size of the horizontal movement, and the presence of a fast horizontal component was not able to increase the size of the small, slow vertical component. Therefore, in our analyses, we pooled horizontal and vertical components of oblique saccades with purely horizontal and vertical saccades, respectively. In normal subjects gain values for downward saccades were greater than for upward saccades and horizontal saccades ($P < 0.0001$); an asymmetry of the gains of up and down saccades has been previously noted (Collewijn *et al.*, 1988b). In the patients, the gain values of vertical saccades was significantly lower compared to horizontal ($P < 0.0001$). Downward saccades had a lower gain than upward saccades ($P < 0.0001$). When we compared patients with normals, we found no significant difference for the gain of horizontal saccades. Gains of upward and downward saccades were significantly lower in the patients than the normals ($P < 0.0001$).

These differences in the peak velocity, duration, and gain of vertical and horizontal saccades in the three affected sisters caused striking changes in the *trajectories of oblique saccades*. Patients showed strongly curved trajectories, but only mild curving of oblique saccades occurred in normal subjects (Fig. 5). Measurements of the saccadic trajectory are summarized in Table 2. Since it was always the vertical component of the oblique saccades that was deficient in the patients, we present

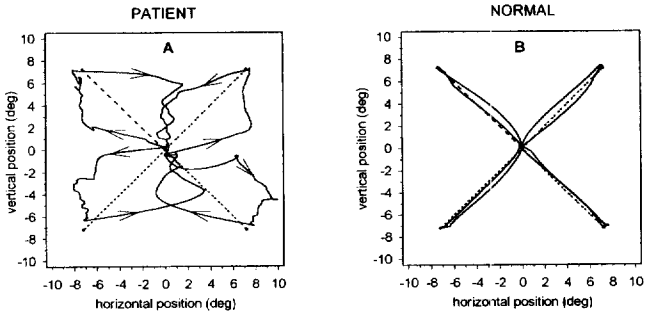

FIGURE 5. Comparison of trajectories of oblique saccades made to and from four target positions starting at primary position in Patient 1 and Subject 2. Arrowheads indicate the direction of eye movement. The trajectory of the target jump is shown as a dotted line. The trajectories of the patient's saccades are strongly curved, reflecting the initial, faster, horizontal component and the later, slower vertical component. To demonstrate clearly these findings, we selected saccades with reached angles that were close to target requirements.

TABLE 2. Trajectories of oblique saccades and smooth pursuit initiation*

	Patients	Normals
Angles of oblique saccades		
Up, initial vertical deficit	34.13†‡ (20.41/42.44)	−1.75 (−19.57/30.25)
Down, initial vertical deficit	39.96†‡ (−5.09/50.79)	2.59 (−22.11/29.24)
Up, final vertical deficit	23.31†‡ (−10.66/35.10)	−0.15 (−13.01/7.30)
Down, final vertical deficit	34.92†‡ (−4.07/49.49)	−1.71 (−22.11/29.24)
Up, reached vertical deficit	2.10†‡ (−2.33/11.88)	−0.11 (−10.66/11.20)
Down, reached vertical deficit	7.57†‡ (−2.43/34.93)	−0.01 (−3.81/6.73)
Angles of smooth pursuit		
smooth vertical deficit	2.02 (−29.11/13.85)	2.50 (−15.91/10.93)
catch−up vertical deficit	12.38† (−5.73/35.71)	1.65 (−18.88/6.99)

*Values shown are medians (range) of vertical deficits (see text for definition).
†Difference between normals and patients was significant, $P < 0.0001$, Mann–Whitney rank sum test.
‡Difference between vertical deficit of upward and downward saccades in patients was significant, $P < 0.0001$, Mann− −Whitney rank sum test.

measurements of the 'vertical deficit': the difference between the target trajectory and the net trajectory of the saccade, measured starting from the horizontal boundary of the quadrant of movement. For example, in response to a 45 deg oblique target jump (up and to the right), the *initial angle* of the saccade (measured from position at time of onset to position at time at peak velocity) was typically about 10 deg from the horizontal (a 35 deg vertical deficit). The *final angle* (from position at onset to position when both horizontal and vertical saccadic components ended) was always closer to the target requirements, being about 20 deg from the horizontal (a 25 deg vertical deficit). [Note, however, that the saccades shown in Fig. 5(A) were selected because the reached angle was close to target requirements and so demonstrated the abnormal trajectory most clearly.] After the first saccade, further corrective saccades and drifts occurred that brought the eye closer to the required position. We measured this *reached angle* at the position where both horizontal and vertical components of the movement stopped. Sometimes, corrective movements were interrupted by the next saccade (a target jump occurred every 1.5 sec). The reached angle was consistently nearest to the required angle being about 43 deg for a 45 deg stimulus angle (a vertical deficit of 2 deg). We found that initial, final and reached vertical deficits were almost identical in response to 10 or 20 deg target jumps. For the normals the vertical deficits were close to zero, indicating that the angle of the oblique saccades was appropriate with respect to the target. Normal subjects did show a small decrease in range from initial to final vertical deficit, reflecting mild, convex or concave, curving of the trajectory. On the other hand, patients showed a significant ($P < 0.0001$) improvement from initial to final angle and their saccades were always curved and always convex with respect to the horizontal plane. We found a significantly greater (initial, final, reached) vertical deficit in downwards rather than in upwards saccades for the patients (Table 2).

Results of analysis of saccadic *latency* are summarized in Table 1. In the normal subjects, the latency of purely horizontal saccades was slightly shorter than of purely vertical saccades (median 148 vs 160 msec); this difference was not significant. The patients had sig-

TABLE 3. Summary of gains of sinusoidal pursuit and responses to active head rotation

Pursuit	Patient 1	Patient 2	Patient 3	Normal 1	Normal 2	Normal 3
hor. sine	0.93	0.86	0.96	0.93	0.93	0.98
ver. sine	0.86	0.54	0.84	0.61	0.87	0.86
obl. 1 hor.*	0.93	0.72	0.91	0.89	0.92	0.96
obl. 1 ver.	0.88	0.66	0.89	0.72	0.87	0.85
obl. 2 hor.†	0.92	0.80	0.97	0.93	0.98	0.99
obl. 2 ver.	0.82	0.65	0.85	0.79	0.87	0.87
ROTF hor.	1.00	1.01	0.99	0.91	1.01	1.04
ROTD hor.	0.99	0.92	0.97	0.79	0.98	1.01
ROTF ver.	1.05	1.07	1.03	0.82	1.05	1.02
ROTD ver.	1.01	1.05	1.01	0.72	0.98	0.97

*Target moves from top right to bottom left and back.
†Target moves from top left to bottom right and back.
hor, horizontal; ver, vertical; obl, oblique; ROTF, active head rotation during visual fixation of stationary target; ROTD, active head rotation in darkness.

nificantly shorter latencies for purely horizontal saccades than for purely vertical saccades (median 120 vs 150 msec, $P < 0.0001$). Patients showed a significantly shorter latency for horizontal saccades than did normal subjects (120 vs 148 msec, $P < 0.0001$). The median of the latency for vertical saccades also was slightly lower in the patient group, but this difference was not significant.

Smooth pursuit

The gains of *sinusoidal smooth pursuit* are summarized in Table 3. Normals and patients had mildly lower gains for vertical or vertical components of pursuit compared to horizontal or horizontal components. Only patient 3 had a slightly worse performance than the normals in both horizontal and vertical direction. Because of the large difference between the horizontal and vertical components of oblique saccades, we focussed our analysis on the trajectory of smooth pursuit initiation in response to oblique *step-ramp stimuli*. In normal subjects, there was no significant difference in the presaccadic acceleration, maximum velocity, and postsaccadic velocity between horizontal and vertical pursuit components; only the gain of catch-up saccades was greater in the vertical than the horizontal plane. Interestingly, the three patients showed significantly greater median presaccadic acceleration (59.1 vs 40.2 deg/sec^2), maximum velocity (11.4 vs 9.3 deg/sec), and postsaccadic velocity (10.5 vs 8.0 deg/sec) of vertical compared with horizontal components ($P < 0.05$). An example is shown in Fig. 6. As expected, the patients' median gain of vertical catch-up saccades (0.8) was significantly less ($P < 0.001$) than that of horizontal catch-up saccades (1.3). When we compared subjects and patients, the 'vertical deficit' of the trajectory of the pursuit movements was not significantly different (Table 3). On the other hand, the 'vertical deficit' for catch-up saccades was significantly greater in the patients ($P < 0.01$). When measurements of smooth pursuit onset from the three patients were compared with those of normal subjects, vertical maximum and postsaccadic velocity were greater in patients than in normals ($P < 0.05$). We found that the latency to onset of smooth pursuit of patients in both planes was shorter than for the control subjects (211 vs 237 msec, $P < 0.0001$).

Gaze stability during active head rotations

The gains of compensatory eye movements during active horizontal or vertical head rotations either while in darkness or during visual fixation of the stationary target (Table 3) were similar for all patients and Subjects 2 and 3. Subject 1 had slightly lower values reflecting his being a myope who habitually wears −3 diopters spectacles. Gain values >1.0 are explained by the target being closer than optical infinity (Huebner *et al.*, 1992). Thus, although vestibular, visual, neck-proprioceptive and other, nonreflexive factors may have contributed to the generation of eye movements during our test conditions, the present results from patients and subjects are consistent with prior studies of eye movements made during active head rotations (Grant *et al.*, 1992).

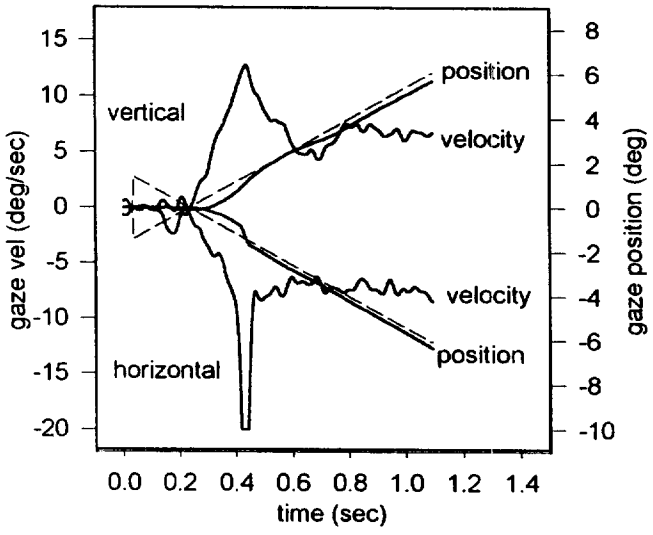

FIGURE 6. Example of response of Patient 2 to oblique (up and to left) step-ramp stimulus (– – –), showing greater initial smooth velocity for the vertical component.

Vergence eye movements

Patients 1–3 achieved convergence angles of 18.4, 21.3, and 35.0 deg, respectively.

DISCUSSION

We provide the first precise measurements of the disturbance of gaze that occurs in NPC. We found that vertical saccades were principally affected but that other eye movements were largely spared. To examine the significance of these findings, first, we summarize the main findings and relate the saccadic abnormalities to the known neural substrate for these movements. Second, we refer to current models for saccade generation, using our data to test some of their predictions, especially those concerning the properties of oblique saccades. Third, we review neuropathological evidence that may have some bearing on these hypotheses. Finally, we comment on how patients such as ours may show adaptive strategies to compensate for their selective deficits.

Putative neural substrate for observed defects

All three affected sisters showed vertical saccades that were slow and hypometric. The defect was greater for downward than for upward movements, as previously reported (Cogan *et al.*, 1981a,b). Horizontal saccades were similar to those of our control subjects. Smooth pursuit and vestibular eye movements were normal in both planes and vergence eye movements were preserved, implying that the defect was not one affecting ocular motoneurons, visual, or vestibular mechanisms. Although the peak velocity of vertical saccades was greatly reduced, we found that the timing of peak velocity was only slightly later (8–10 msec) for vertical than for horizontal movements. Furthermore, the latency to onset of saccade generation in response to visual stimuli was not prolonged in our patients (it may even have been

reduced, a possible adaptive strategy that is discussed below). These findings indicate that the mechanism that *initiates* saccade generation was normal. It is presently thought that the ocular motoneurons receive the command for horizontal saccadic eye movements from so-called burst neurons in the paramedian pontine reticular formation (PPRF) and the command for vertical saccades from burst neurons in the rostral interstitial nucleus of the medial longitudinal fasciculus (riMLF), which lies in the prerubral fields of the rostral midbrain (Strassman *et al.*, 1986a,b; Büttner-Ennever, 1988; Leigh & Zee, 1991). Both sets of saccadic burst neurons are held in check by omnipause neurons that lie in the nucleus raphe interpositus (RIP) of the pons (Büttner-Ennever *et al.*, 1988; Langer & Kaneko, 1990); they have been shown to be glycinergic (Horn *et al.*, 1994). The omnipause neurons are so called because they pause their inhibitory discharge for all saccades, horizontal or vertical. Thus, our findings of *selective slowing* of vertical saccades, but *normal onset* of saccades in both planes is evidence against involvement of omnipause neurons in our patients.

During attempted oblique saccades, several useful comparisons could be made between the horizontal and vertical components. First, although the time from onset to peak velocity was similar, the horizontal peak velocity was much greater so that the initial trajectory of these eye movements was close to horizontal in our patients; this suggests that although burst neurons in the PPRF and riMLF came on at the same time, the output of the latter was weak. Thus, it seems likely that the burst cells of the riMLF were directly affected by NPC, a selective vulnerability that is discussed further below. Why downward saccades were more affected than upward is more problematic, although destructive lesions of riMLF, such as infarcts, may produce greater defects of downward than of upward saccades (Büttner-Ennever *et al.*, 1982). A second finding was that, during oblique saccades, the eye usually completed the horizontal component of its movement much before the vertical component ended. This resulted in the overall trajectory of the saccade as being very curved (Fig. 5). After the eye completed its horizontal component, it was not completely still, but often oscillated around the horizontal end-position at 10–20 Hz until the vertical component was complete (Fig. 4). A third finding was that the gain of vertical saccades in our patients, especially downward, was reduced. The gain of horizontal saccades was similar in patients and normal subjects. This difference between saccadic gain in the horizontal and vertical planes suggests that an inappropriate 'motor error' signal (such as desired change in eye position) was not the cause of the vertical hypometria; a more likely and parsimonious explanation is that disease of the vertical burst neurons in riMLF accounted for decreased velocity, decreased gain, and prolonged duration.

The selective nature of the defect was most evident when smooth pursuit initiation was tested with step-ramp stimuli moving in a diagonal trajectory. The initial eye movement had similar horizontal and vertical components so that the trajectory of pursuit initiation was close to 45 deg, which is similar to the normal subjects (Fig. 6). Thus, the trajectory of saccades (including catch-up saccades) and smooth pursuit initiation differed greatly (Table 2).

Ability of saccadic models to account for present findings

To further investigate the putative role of the vertical burst neurons in NPC, we tested a current model for saccade generation. Requirements of this model were:

1. That vertical, but not horizontal, saccades be slow.
2. That saccades be generated at normal latencies in both the horizontal and vertical planes.
3. That the trajectories of oblique saccades be strongly curved.
4. That both components of oblique saccades start at the same time, but the vertical component outlast the horizontal.
5. That the after completion of the horizontal component, the eye oscillate horizontally while the vertical component is completed.

Because it had been reported to successfully simulate *human* saccades, we chose the model of Zee *et al.* (1992); this is presented in a simplified scheme in Fig. 7. In this scheme, a motor error signal (the difference between desired and actual change in eye position) drives burst neurons to produce a saccadic velocity command. The latter is integrated so that an efference copy of the change in eye position is fed back, possibly through the superior colliculus, to be compared with desired change in eye position (Jürgens *et al.*, 1981; Keller & Edelman, 1994; Kustov & Robinson, 1995); the difference is the motor error. Thus, the nonlinear relationship between motor error and burst neuron discharge is important in determining saccade dynamics (Van Gisbergen *et al.*, 1981); other factors are the mechanical properties of the eyeball, and the premotor pathways ('pulse-slide-step') that take account of them [see Zee *et al.* (1992) for discussion of this]. Since our patients showed near-normal nonsaccadic eye movements, we infer that the properties of the premotor pathways, eye muscles and eyeball were unaffected, and that dysfunction of the vertical burst neurons were responsible for their abnormal saccades. We found that the model closely simulated horizontal and vertical saccades of normal subjects, and horizontal saccades of our patients [Fig. 8(A and B)]. Furthermore, by simply changing two parameters of the burst neuron discharge curve, we could also simulate most dynamic characteristics of our patients' vertical saccades [Fig. 8(C and D)]. To enable the model to accurately simulate our patients' slow vertical saccades, we reduced the asymptotic value of the burst response curve, based on the values shown in Table 1; a comparison of the horizontal and vertical burst neuron curves is shown in Fig. 7(B). To produce saccadic hypometria and account for the 8–10 msec difference between the timing of peak velocity of horizontal and

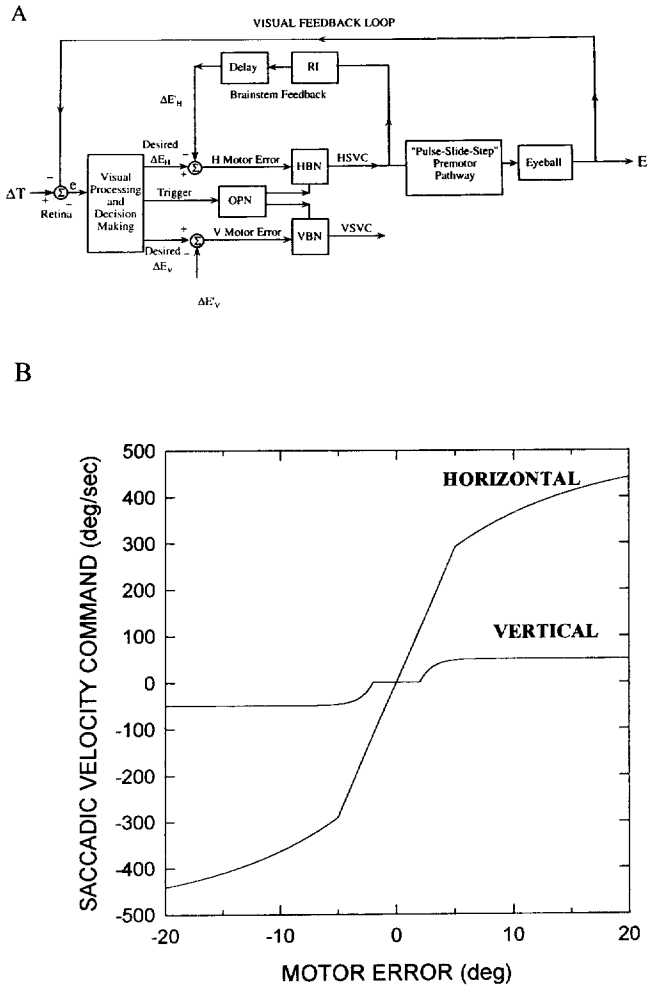

FIGURE 7. (A) Model of brainstem generator for oblique saccades. A change in target position (ΔT) is compared with current eye position (E) at the retina to give retinal error (e). The latter is subject to visual processing and decision making to generate the signals specifying the size of a saccade (desired change in eye position) and the trigger signal that turns omnipause neurons (OPN) off and allows both horizontal bursts neurons (HBN) and vertical burst neurons (VBN) to commence discharge. For an oblique saccade, the desired changes in horizontal and vertical eye movements are fed to the independent horizontal and vertical saccade generators; for simplicity, only the horizontal is shown in full. The desired change in horizontal eye position (Desired ΔE_H) is compared, at the summing junction, with current change in eye position ($\Delta E'_H$) to obtain the horizontal motor error (H motor error); this error signal drives HBN to produce a horizontal saccadic velocity command (HSVC). The latter is fed back through a resettable integrator (RI) and a delay so that an efference copy of the change in eye position can be compared with the desired change in eye position. A vertical motor error signal is similarly obtained by comparing desired change in vertical eye position (Desired ΔE_V) and current change in eye position ($\Delta E'_V$); the VBN produce a vertical saccadic velocity command (VSVC). Both saccadic velocity commands are passed through a 'Pulse-Slide-Step' premotor pathway that takes account of the mechanical properties of the eyeball [see Zee *et al.* (1992) for discussion of this and list of parameter values]. (B) The characteristics of the nonlinear relationship between motor error and the saccadic velocity commands for HBN (HORIZONTAL) and VBN (VERTICAL); it is these relationships that determine the dynamic properties and trajectories of oblique saccades. Note that the vertical curve has a lower asymptote and 'dead-zone' for motor errors < 2 deg. Curves shown correspond to saccadic amplitude/peak velocity relationships of Patient 3 (see Results), with V_{max} at 442 deg/sec horizontally and 51 deg/sec vertically, and C at 9.44 horizontally and 1.03 vertically.

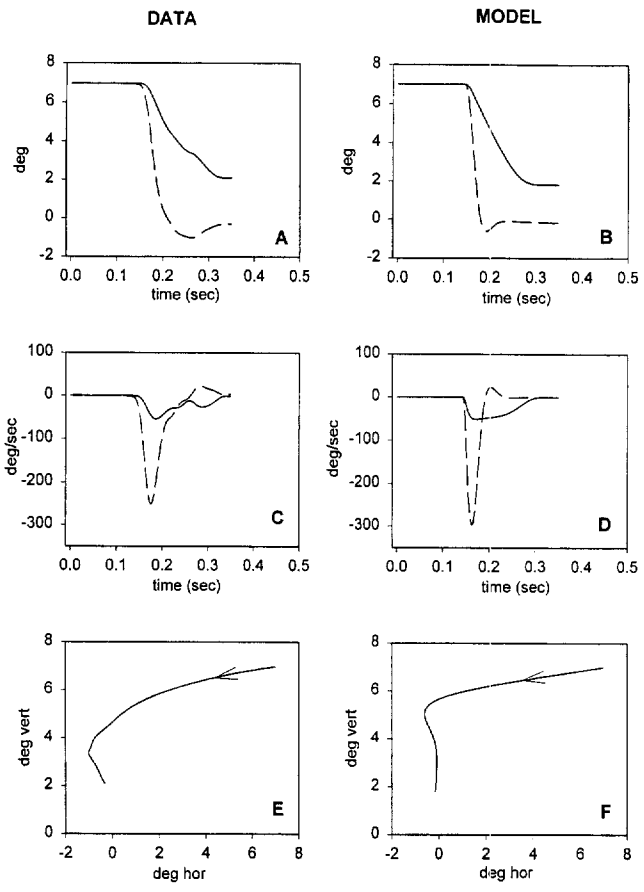

FIGURE 8. Comparison of a representative oblique saccade from Patient 3 (DATA) and predictions of the model shown in Fig. 7 (MODEL). (A) and (B) are position–time plots, (C) and (D) are velocity–time plots, and (E) and (F) are horizontal–vertical trajectory plots (arrowheads indicate the direction of the movement in response to target step down and to the left). Based on the complete pool of saccades from Patient 3, we set the velocity asymptotes to 442 deg/sec for horizontal and 51 deg/sec for vertical saccades. Note how the model accounts for both the hypometria and slowing of the vertical component, and the overall trajectory of the saccade. For (A)–(D), dashed line represents horizontal and solid line represents vertical trace.

vertical saccade components, we changed the intercept of the curve to produce an effective 'dead zone' when small motor errors (< 2 deg) caused no burst cell output. When we combined two versions of the model—one set to simulate horizontal and the other vertical saccades in our patients—in a simple Cartesian addition, the simulated trajectory of the oblique saccade [Fig. 8(D and E)] was similar to that observed in our patients (Fig. 5), including the initial and final angle, and the tendency of the horizontal movement to show small oscillations while the vertical component was being completed.

We also considered alternative models, especially that proposed by Scudder (1988). However,

1. This model does not readily oscillate.
2. It does not account for the characteristic nonlinear relationship between the peak velocity and amplitude of saccades.

3. It has a topology inconsistent with recent evidence suggesting that the superior colliculus is part of the saccadic feedback pathway (Waitzman *et al.*, 1991).
4. It produces slowing of *both* horizontal and vertical saccades when omnipause (not burst) neurons are experimentally lesioned (Kaneko, 1989; Kaneko & Fuchs, 1987; Kaneko, 1992).

Possible effects of omnipause cell disease in humans are briefly discussed in the next section. An important issue in modeling oblique saccades is whether there is independent feedback control of horizontal and vertical saccadic components (Bahill & Stark, 1977; Grossman & Robinson, 1988) or single vectorial feedback (Optican, 1994; Van Gisbergen *et al.*, 1985). An important way to distinguish these models is to determine whether the horizontal and vertical components end at separate times or whether the duration of the shorter component is 'stretched' (Grossman & Robinson, 1988). Although some stretching of horizontal components of oblique saccades was evident in our patients [compare Fig. 3(A) and Fig. 3(B)], this was often not enough to prevent the horizontal component from ending first. In the latter case, small horizontal oscillations were evident (Fig. 4) and we postulate that this was because the omnipause neurons were still silent, and the oscillations reflected the known instability of the burst neurons (Zee & Robinson, 1979; Van Gisbergen *et al.*, 1981). This evidence, in addition to recent studies of monkey superior colliculus by Nichols and Sparks (1995), supports the notion of separate local feedback control of horizontal and vertical components of oblique saccades. Although we did not attempt to simulate stretching of horizontal saccadic duration during oblique saccades, this could probably be achieved, while still preserving separate feedback pathways, using cross-coupling of either the saccadic generators (Grossman & Robinson, 1988) or their inputs (Becker & Jürgens, 1990).

Neuropathological evidence related to present hypothesis

Direct histopathological evidence to support our hypothesis is currently lacking, since the anatomical basis for vertical saccadic eye movements rests on fairly recent studies [see Büttner-Ennever (1988) for a review]. One report contains a personal communication of "a greater degree of neuronal ballooning in the mesencephalon as compared with other brainstem areas" (Higgins *et al.*, 1992). In Gaucher's disease, which is characterized initially by selective impairment of voluntary gaze in the *horizontal plane* (Patterson *et al.*, 1993b; Winkelman *et al.*, 1983), the brain shows neuronal loss and gliosis restricted to the cerebellum and the brainstem, including the midline where the omnipause and inhibitory burst neurons cross (Büttner-Ennever, Personal Communication, 1994). As noted above, experimental lesions of the omnipause neurons are reported to cause slowing of both horizontal and vertical saccades (Kaneko, 1989; Kaneko & Fuchs, 1987; Kaneko, 1992), even though it had been previously postulated that such lesions would lead to saccadic oscillations (Zee & Robinson, 1979). In humans, Ridley *et al.* (1987) were unable to demonstrate histopathological changes in omnipause neurons in two patients with saccadic oscillations. However, a more recent immunopathological study of a patient with saccadic oscillations in association with cancer demonstrated complete absence of cells in the omnipause region (Hormigo *et al.*, 1994). Thus, it remains possible that lesions restricted to omnipause cells may cause saccadic oscillations and, for the reasons previously given, it seems more likely that dysfunction of burst, rather than omnipause, neurons is responsible for slow vertical saccades in NPC.

Evidence for adaptive changes of eye movements in NPC

We have been able to identify a more selective defect than previous reports of NPC, which have not attempted to quantify the performance of each functional class of eye movements but have emphasized the progressive and relentless progression to eventually restrict all voluntary gaze (Neville *et al.*, 1973; Cogan *et al.*, 1981a,b). One surprising finding was that our patients showed several properties that, perhaps, were superior to those of the control subjects. First, the horizontal saccades of the patients showed a significantly shorter latency than the control subjects. Although our patients' vertical saccades had longer latencies compared to their horizontal movements, this might be partly because of technical difficulties in detecting the onset of vertical saccades which, since they were slow, tended to reach the threshold criterion for onset (15 deg/sec) later. In fact, the median latencies of both vertical and oblique saccades were slightly shorter in the patients than in the normals. Second, the latency to onset of pursuit was decreased in patients compared with controls. Third, in the patients, the presaccadic acceleration and maximum velocity of vertical smooth pursuit onset was increased compared with horizontal pursuit onset; some normal subjects are reported as showing the former but not the latter (Rottach *et al.*, 1996). Finally, we noted that "anticipatory drifts" (Kowler & Steinman, 1979) frequently preceded saccadic responses. Taken together, these findings suggest that the selective involvement of the ocular motor system in NPC allows the brain to make adaptive changes of one system (vertical smooth pursuit) to partially compensate for deterioration of another system (vertical saccades). We are unaware of prior demonstration of such changes, which might assume greater significance if the progression of the underlying disease could be arrested.

Clinical implications

Our findings may have some bearing on biochemical and therapeutic aspects of NPC. First, the nature of the selective defect of ocular motility in the earlier stages of this disease points to dysfunction of a specific population of cells—vertical burst neurons. Studies to determine what metabolic properties of these cells makes them selectively vulnerable might shed light on the nature of

neuronal injury in this disorder. Second, we suggest that the effectiveness of new treatments for NPC (Patterson *et al.*, 1993a) could be monitored by serial measurements of eye movements, since they can be recorded more precisely than limb movements or gait, and the technique is certainly less invasive than repeated liver biopsy.

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